ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Dextromethorphan/quinidine for the treatment of bulbar impairment in amyotrophic lateral sclerosis

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Received: 14 April 2023; Revised: 10 May 2023; Accepted: 19 May 2023

***Annals of Clinical and Translational Neurology* 2023; 10(8): 1296–1304**

doi: 10.1002/acn3.51821

Abstract

Objective: No efficacious treatments exist to improve or prolong bulbar functions of speech and swallowing in persons with amyotrophic lateral sclerosis (pALS). This study evaluated the short-term impact of dextromethorphan/quinidine (DMQ) treatment on speech and swallowing function in pALS. **Methods**: This was a cohort trial conducted between August 2019 to August 2021 in pALS with a confirmed diagnosis of probable-definite ALS (El-Escorial Criteria-revisited) and bulbar impairment (ALS Functional Rating Scale score ≤ 10 and speaking rate ≤ 140 words per minute) who were DMQ naïve. Efficacy of DMQ was assessed via pre-post change in the ALS Functional Rating Scale-Revised bulbar subscale and validated speech and swallowing outcomes. Paired *t*-tests, Fisher's exact, and χ^2 tests were conducted with alpha at 0.05. **Results**: Twenty-eight pALS enrolled, and 24 participants completed the 28-day trial of DMQ. A significant increase in ALSFRS-R bulbar subscale score pre- (7.47 ± 1.98) to post- (8.39 ± 1.79) treatment was observed (mean difference: 0.92, 95% CI: 0.46–1.36, $p < 0.001$). Functional swallowing outcomes improved, with a reduction in unsafe (75% vs. 44%, $p = 0.003$) and inefficient swallowing (67% vs. 58%, $p = 0.002$); the relative speech event duration in a standard reading passage increased, indicating a greater duration of uninterrupted speech (mean difference: 0.33 s, 95% CI: 0.02–0.65, $p = 0.035$). No differences in diadochokinetic rate or speech intelligibility were observed ($p > 0.05$). **Interpretation**: Results of this study provide preliminary evidence that DMQ pharmacologic intervention may have the potential to improve or maintain bulbar function in pALS.

Introduction

Progressive degeneration of bulbar musculature results in dysphagia (swallowing impairment) and dysarthria (speech impairment) in people with ALS (pALS). Regardless of disease onset type, bulbar dysfunction impacts 93% of pALS at some point throughout the disease course[1,2] with pALS rating the inability to communicate as the worst disease symptom.[3] Progressive dysarthria and dysphagia contributes to malnutrition, social isolation, increased caregiver burden, compromised pulmonary function, and increased mortality in ALS.[4–6] Despite these sequelae, treatment targeting bulbar dysfunction in ALS are lacking with routine use of the current palliative standard of care management approaches. This includes compensatory approaches such as dietary and environmental modifications, feeding tube placement, and alternative and assistive communication interventions that are implemented reactively once dysarthria or dysphagia manifest and are clinically detected.[7,8] The lack of targeted

treatment options to proactively improve or maintain bulbar function represents a crucial clinical management gap in the care of pALS.[9–11] To date, no efficacious treatments have been identified to prolong safe and efficient oral intake or functional communication in pALS.[7]

The need for clinical trials to improve treatment options and bulbar symptom management for pALS has been called for by the Northeastern ALS (NEALS) Consortium Bulbar Subcommittee.[12] Recent excitement has surfaced regarding the therapeutic potential of a pharmacologic intervention, Nuedexta (20 mg dextromethorphan HBr/10 mg quinidine sulfate, DMQ), for the treatment of bulbar dysfunction in pALS. Subsequent to FDA approval of DMQ for the treatment of pseudobulbar affect in 2010, anecdotal reports of improved bulbar dysfunction in pALS prescribed DMQ have emerged.[13] Subsequently, a Phase II multicenter, double-blind, randomized crossover trial in 60 pALS treated with DMQ for 28 days (±3 days) was conducted with results highlighting patient-reported improvements in speech, swallowing, and salivation following DMQ treatment.[13,14] The inclusion of objective speech and swallowing physiologic outcomes is particularly important when examining effects of DMQ, given that it contains selective serotonin reuptake inhibitors (SSRIs), impacting regulation of emotional expression, feelings of well-being and the modulation of depression.[15] Although the seminal trial by Smith and colleagues represents a great contribution to the field, the primary outcome was a patient-reported tool without the inclusion of validated clinical or physiologic outcomes of speech or swallowing function.[13] Furthermore, the second published report from this study including physiologic speech outcomes was from a small cohort of 10 pALS participants from the original study.[14] In the present study, we sought to evaluate the impact of a 28-day course of DMQ treatment on bulbar symptomology and objective speech and swallowing physiologic outcomes in pALS.

Methods

Participants

An open-label cohort pilot trial was conducted across two sites (University of Florida, Gainesville and the Phil Smith Neuroscience Institute at Holy Cross Health, Fort Lauderdale). Institutional review board approval was obtained at each site and all enrolled participants provided informed written consent. Participants were provided with the study drug at no charge. Due to the nature of this funding mechanism, no participant compensation was provided. The study was conducted in good clinical compliance (NCT#03883581) and in accordance with the Declaration of Helsinki.

The study was conducted between August 2019 and August 2021 across two ALS clinical trial sites recognized by the ALS Association (ALSA) and NEALS. Participant enrollment and data collection occurred at a single site (Phil Smith Neuroscience Institute), and the secondary site (University of Florida) performed all blinded data analysis by research personnel not involved in data collection. Inclusion criteria to participate in this study were: (1) a confirmed diagnosis of probable or definite ALS (El-Escorial Criterion revisited)[16] by a fellowship-trained and board-certified neurologist; (2) Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised[16] bulbar subscore <10; (3) speaking rate of ≤ 140 words per minute (wpm); (4) no treatment with DMQ in the past; (5) have no allergies to barium sulfate or the components of DMQ. Exclusion criteria were: (1) treatment for sialorrhea (i.e., glycopyrrolate, scopolamine patch, and botulinum toxin) in the past 3 months or any history of radiation therapy to the salivary glands; (2) tracheostomy; (3) diagnosis of advanced frontotemporal dementia per the treating neurologist; (4) nil per oral feeding status; (5) concurrent participation in an interventional clinical trial. Furthermore, individuals taking riluzole or edaravone were required to be on a stable dose for a minimum of 30 days prior to enrollment. Potential participants were screened for eligibility and those meeting criteria signed an informed consent and were enrolled. Enrolled participants completed a baseline bulbar assessment and immediately commenced DMQ treatment for a 28-day period and returned to the laboratory within a 2-day window (medication was continued until the evaluation) for the post-treatment bulbar assessment (Fig. 1).

Intervention

DMQ is an FDA approved medication with a well-documented safety profile.[15] On treatment days 1–7, participants took DMQ once daily at the same time. On days 8–28, participants took two capsules per day at 12-h intervals. DMQ was provided in four individual, factory-sealed bottles each containing 13 red brick gelatin capsules.

Primary outcome

The primary endpoint was change in the rater-administered ALSFRS-R bulbar subscore. This outcome is comprised of three questions specific to speech, swallowing, and salivation rated on a 5-point ordinal scale (0 to 4). Total ALSFRS-R bulbar subscores range from 0

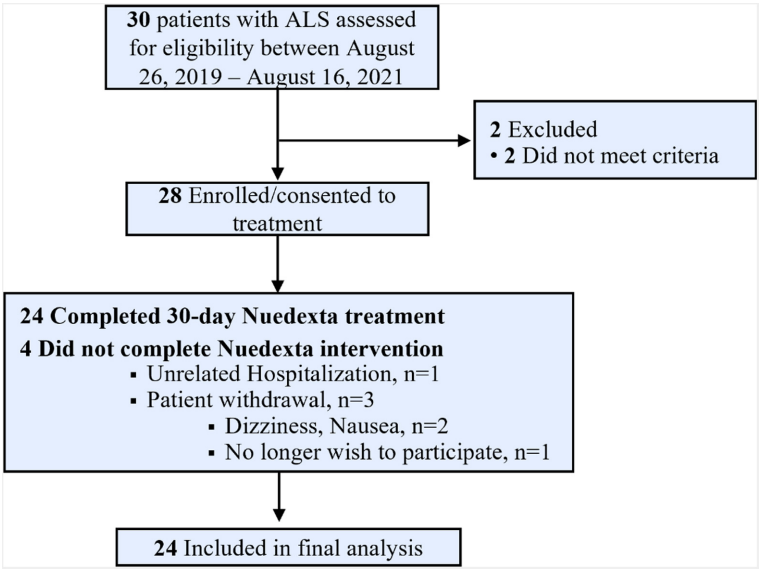

Figure 1. CONSORT flowchart of study recruitment and enrollment for the clinical trial NCT0388358. ALS, amyotrophic lateral sclerosis.

indicating a total loss of bulbar function to 12 indicating no bulbar symptoms.

Swallowing outcome

Participants underwent a standardized videofluoroscopic evaluation of swallowing to directly visualize bolus flow (Shimadzu Flexavision R3 R/F, Torrance, CA). With the participant comfortably seated, images were captured continuously at a rate of 30 frames per second (FPS) in high resolution using a TIMS Dicom Audiovisual recording system for subsequent offline analysis (Version 3.2, TIMS Medical, TM, Chelmsford, MA). A standardized 10-item bolus protocol using Varibar barium sulfate products (Bracco Imaging, Monroe Township, NJ), mapped to International Dysphagia Diet Standardization Initiative (IDDSI)[17] levels was used and included: one saliva swallow, three 5 cc thin liquid boluses (IDDSI level 0), one comfortable cup sip of thin liquid from a 90 cc cup (IDDSI level 0), a serial drinking challenge with the remaining thin liquid from the 90 cc cup (IDDSI level 0), two 5 cc pudding trials (IDDSI level ≥4), ¼ graham cracker coated with pudding (IDDSI level 7), and a 13 mm barium tablet (EZ-Disk). To ensure participant safety, a bailout criterion was strictly enforced with the swallowing evaluation terminated immediately following three episodes of uncleared aspiration.[18–20]

Swallowing function was assessed using the validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scale.[21,22] The DIGEST scale measures both airway safety (safety grade) and pharyngeal residue (efficiency grade) on each bolus trial to derive an overall composite DIGEST grade (Table 2). Raw data and established dysphagia binary thresholds were used (dysphagia = DIGEST ≥ 1, no dysphagia = DIGEST = 0).[21,23] Expert raters were blinded to participant and evaluation time point.

Speech outcome

Participants completed a series of speech assessments while comfortably seated in front of a MacBook Pro computer (Apple, Inc.). A condenser headset microphone (AKG, Inc., HSC271) with a lapel windscreen (eBoot, Inc.) was positioned approximately five centimeters from the participant's right labial crease and connected to a digital audio recorder (TASCAM, DR40) for subsequent offline analysis using Audacity (Audacity, Inc.). Speech assessment included: the standardized Bamboo Passage,[24] the Sentence Intelligibility Test,[25] an alternating motion rate (AMR) test in which participants are asked to repeat /ba/ and /ta/ as quickly and clearly as possible on a single breath, and a maximum phonation task using /ah/. The speech outcomes derived from each test are described in Table 2.

Patient-reported outcome

Participants completed two validated patient-reported outcomes at each evaluation. The Center for Neurological Study Bulbar Function Scale (CNS-BFS) is a 21-item patient-report scale indexing degree of bulbar dysfunction in the domains of speech, salivation, and swallowing ranging from 21 (no bulbar impairment) to 112 (severe bulbar impairment).[26] The Eating Assessment Tool-10 is

a 10-item self-report scale indexing an individuals perceived level of swallowing impairment ranging from 0 (no impairment) to 40 (severe impairment).[27]

Statistical analyses were completed using JMP (V16.1.0, SAS, Inc.). Measures were summarized as mean and standard deviation (continuous) or count and percentage (binary). Normality was evaluated using quantile plots and the Shapiro–Wilk goodness-of-fit test. Missing data were handled via pairwise deletion. To assess the impact of DMQ on swallowing and speech outcomes and PRO metrics, a two-sided paired *t*-test (parametric data) and a Fisher's exact or χ^2 test (non-parametric data) were conducted with alpha set at 0.05. Mean differences were calculated and reported with 95% confidence intervals. Due to pilot nature of this study, no correction for multiple comparisons was performed.

Results

Study participants

Between August 2019 and August 2021, 30 pALS were screened for enrollment, of which 28 meet the inclusion criteria (Fig. 1). A summary of participant demographics and disease characteristics are summarized in Table 1. Drug compliance was >90% based on patient reported drug logs.

Table 1. Baseline demographics and clinical characteristics for all study participants.

Baseline characteristics	Total
Male sex, no. (%)	17 (61)
Age, mean (SD), years	64.75 (9.18)
Race	
Black	2 (8)
Caucasian	21 (84)
More than once race reported	2 (8)
Ethnicity, non-Hispanic or Latino, no. (%)	23 (92)
Disease duration (symptom onset), mean (SD), months	40.45 (49.83)
ALSFRS-R total score, mean (SD)	32.07 (8.37)
ALS type, no. (%)	
Familial, C9orf72+	2 (8)
Sporadic	15 (60)
Unknown	8 (32)
Concomitant riluzole use, no (%)	10 (40)
Concomitant edaravone use, no (%)	3 (12)
Disease onset type, no. (%)	
Bulbar	12 (42.86)
Spinal	14 (50.0)
Mixed	2 (7.14)

Data expressed as means (standard deviation) or frequency count. Disease duration expressed as months from symptom onset, FVC presented as percent predicted.
ALSFRS-R, ALS Functional Rating Scale-Revised.

A total of four adverse events were reported during study participation (Table 3) including nausea, gastrointestinal discomfort, dizziness, and hospitalization for deep vein thrombosis. The latter was determined to be unrelated to DMQ treatment and resulted in discontinuation of the study drug due to prolonged hospitalization. Results for study outcomes of interest are summarized in Table 4.

Primary efficacy outcome

The ALSFRS-R bulbar subscore significantly increased from 7.50 (SD: 2.00) to 8.41 (SD: 1.79) pre- versus post-treatment, respectively (mean difference: 0.92, 95% CI, 0.49–1.35, $p < 0.001$). Seventy-five percent ($n = 18$) of participants completing the drug protocol improved (increased) in their total ALSFRS-R bulbar subscore, 12.5% ($n = 3$) decreased (worsened), and 12.5% ($n = 3$) remained unchanged.

Secondary physiologic swallowing outcomes

Global dysphagia status improved following DMQ treatment, with the proportion of individuals classified as dysphagic decreasing from 29% to 12% from pre- versus post-DMQ interventions, $p = 0.002$. DIGEST safety and efficiency severity grades improved following treatment, with a reduction in the proportion of unsafe (75% vs. 54%, $p = 0.003$) and inefficient (67% vs. 58%, $p = 0.002$) swallowers pre vs. post DMQ, respectively.

Secondary physiologic speech outcomes

Speech event duration for the bamboo passage reading task increased from pre- to post-treatment time points, indicating a greater duration of uninterrupted speech post-treatment (mean difference: 0.33, 95% CI, 0.02–0.65, $p = 0.035$). The bamboo passage, AMR, and speech intelligibility test outcomes did not differ across testing points, $p > 0.05$ (Table 4).

Patient report outcomes

EAT-10 (mean difference: −1.57, 95% CI, −3.91 to 0.77, $p = 0.18$) and CNS-BFS (mean difference: −1.61, 95% CI, −6.08 to 0.60, $p = 0.10$) scores did not differ pre- to post-DMQ treatment (Table 4).

Interpretation

In this cohort of pALS with mild-to-moderate bulbar disease progression, a 28-day course of DMQ pharmacologic intervention led to improvements in bulbar function. A

Table 2. Study outcome measures.

Domain	Testing procedure	Outcome measure	Derivation
Primary outcome	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R, Cedarbaum et al.[16])	ALSFRS-R bulbar subscore	Sum of speech, swallow, salivation ALSFRS-R items (items 1–3)
Swallow	Dynamic Imaging Grade of Swallowing Toxicity (DIGEST, Hutcheson et al.[21])	1 DIGEST efficiency grade 2 DIGEST safety grade 3 DIGEST total grade	1 Efficiency grade: pharyngeal bolus transport across a series of standardized bolus trials 2 Airway safety grade: frequency and severity of airway invasion across a series of standardized bolus trials 3 Total: interaction score derived from efficiency and safety subscores
Speech	Sentence Intelligibility Test (SIT, Yorkston et al.[25])	Speech intelligibility (%)	Number of spoken words correctly transcribed/ number of total words spoken
	Bamboo Passage (Green et al.[14])	1 Passage duration (seconds) 2 Speaking rate (words per minute) 3 Speech event duration (seconds) 4 Pause event duration (%)	1 Total speech duration (seconds) 2 No. of total words/total speech duration (seconds) 3 Total speech duration (seconds)/No. of speech events 4 Total pause duration (seconds)/No. of pause events
	Alternation motion rate (AMR)	Number of repetitions /ba/ Number of repetitions /ta/	Total number of single syllable repetitions produced as quickly as possible on a single breath
	Maximum phonation time	Maximum duration of /ah/	Total duration of sustained phonation on a single breath
Patient-reported outcomes	Eating Assessment Tool- 10 (EAT-10, Belafsky et al.[27])	EAT-10 total score	Validated 10-item patient report outcome of perceived swallowing impairment
	Center for Neurologic Study Bulbar Function Scale (CNS-BFS, Smith et al.[26])	CNS-BFS total score	Validated 21-item patient report outcome of perceived salivary, speech and swallowing function

Table 3. Adverse study events.

Adverse event characteristics	Treatment, no. events (% participants, # participants)
No AEs reported	21 (84, 0)
Mild	1 (4, 1)
Moderate	2 (8, 2)
Severe	1 (4, 1)
Relationship to study drug	
Not related	1 (4, 1)
Possibly related	1 (4, 1)
Probably related	2 (8, 2)

significant improvement in the ALSFRS-R bulbar subscore was observed in 75% of participants, with 50% ($n = 12$) of pALS improving by one point, 21% ($n = 5$) by two points and 4% ($n = 1$) by three points, suggesting not only a slowing of decline but an improvement in function. Of note, there were no trends across sex, disease duration, onset type or age in participants that were unchanged or demonstrated continued ALSFRS-R bulbar subscore decline following treatment. The ALSFRS-R scale is used extensively as the primary outcome in ALS clinical trials, as it is a strong predictor of survival and declines consistently with disease progression at −0.92 points per month.[28,29] This implies a positive change when compared to the noted monthly historical rate of ALSFRS-R decline (−0.92), and results of previous positive placebo-controlled ALS treatment studies that reflect a between-groups mean difference in the ALSFRS-R total score of 0.20 and 0.42 after 4 and 24 weeks of treatment, respectively.[28,30] These results also corroborate the report by Smith and colleagues in which ALSFRS-R bulbar subscores improved following treatment with a mean difference of 0.60.[13]

Significant improvements in swallowing safety, swallowing efficiency, and speech event duration during a standardized reading passage were also noted. Overall, there were consistent, positive trends in bulbar outcomes observed following treatment. These findings add positive physiologic outcomes to the two existing but limited published studies in this area[13,15] to suggest that pharmacologic treatment with DMQ has a beneficial impact on speech and swallowing physiology in pALS. The findings of this small pilot study demonstrate a promising,

Table 4. Summary of the ALSFRS-R bulbar subscore, swallowing, speech, and patient-report outcomes.

Outcomes	Mean (SD) Pre-DMQ	Post-DMQ	Difference (95% CI)	*p*-value
Primary outcome measure				
ALSFRS-R bulbar subscale score	7.50 (2.0)	8.41 (1.79)	0.92 (0.49–1.35)	0.0002*
Speech secondary outcomes				
SIT speech intelligibility, %	71.52 (29.03)	73.06 (26.80)	1.54 (−5.40 to 8.48)	0.647
Bamboo passage pause duration, %	21.83 (7.43)	19.71 (8.53)	2.23 (−0.27 to 4.52)	0.078
Bamboo passage, speech event duration, s	2.62 (1.43)	2.96 (1.41)	0.33 (0.02–0.65)	0.035*
Bamboo passage duration, s	66.19 (17.24)	65.33 (17.26)	0.86 (−4.30 to 1.66)	0.610
Bamboo passage speaking rate, words per min	93.24 (22.23)	95.08 (24.76)	1.84 (−2.67 to 6.36)	0.406
/ba/ AMR, number repetitions	43.0 (28.29)	46.30 (28.07)	3.30 (−3.83 to 10.44)	0.347
/ta/ AMR, number repetitions	29.08 (18.63)	34.0 (23.34)	4.9 (−0.15 to 9.97)	0.056
Maximum phonation /ah/, s	18.76 (11.79)	18.50 (10.07	1.20 (−2.76 to 2.23)	0.829
Swallowing secondary outcomes				
DIGEST total grade, *n* (%)				0.017*
0 (No dysphagia)	3 (12)	7 (29)		
1–4 (Mild–severe dysphagia)	21 (88)	17 (71)		
DIGEST safety grade, *n* (%)				0.003*
0 (No dysphagia)	6 (25)	11 (46)		
1–4 (Mild–severe dysphagia)	18 (75)	13 (54)		
DIGEST efficiency grade, *n* (%)				0.002*
0 (No dysphagia)	8 (33)	10 (42)		
1–4 (Mild–severe dysphagia)	16 (67)	14 (58)		
Patient report tertiary outcomes				
Eating Assessment Tool- 10, total score	12.26 (9.28)	10.69 (8.27)	−1.57 (−3.91 to 0.77)	0.179
CNS-BFS, total score	56.87 (15.65)	54.13 (14.57)	1.61 (−6.08 to 0.60)	0.103
Sialorrhea	14.58 (6.95)	13.75 (6.31)	0.83 (−3.02 to 4.69)	0.238
Speech	24.25 (6.08)	23.21 (6.93)	1.04 (−2.74 to 4.82)	0.258
Swallowing	18.38 (5.72)	17.5 (4.79)	0.875 (−2.19 to 3.94)	0.212

*$p < 0.05$

clinically meaningful impact on the rate of bulbar disease decline.

DMQ had a robust impact on swallowing function. Global dysphagia frequency decreased by 16% (88% to 71%), with a 21% reduction in the frequency of unsafe swallowing (75% to 54%), and 9% reduction in the frequency of inefficient swallowing (67% to 58%) following treatment. This dataset is the first to examine the impact of DMQ treatment on swallowing using videofluoroscopy, a direct radiographic imaging technique.

Dysarthria in pALS is clinically characterized by slow speaking rate and articulatory rate that ultimately impact speech intelligibility. These secondary speech outcomes were selected to reflect the physiologic bases of these impairments by indexing intelligibility at the systems level (speech intelligibility test), and speech subsystems level (respiratory: bamboo passage; articulatory: DDK).[31] All speech outcomes trended toward improvement in this small dataset; however, the noted significant increase in uninterrupted speech and non-significant reduction in pause duration in 74% of pALS following DMQ intervention illustrate a functional impact on known biomarkers of bulbar motor deterioration. These results also corroborate the findings of Green and colleagues in ten pALS following DMQ treatment.[14] The AMR tasks involve fine motor movements of the tongue to rapidly produce /ba/ (bilabial target) and /ta/ (lingual and alveolar target) and have been shown to precede decline in speech intelligibility in pALS. AMR tasks did not significantly differ across testing time points; however, the /ta/ DDK task, involving rapid, fine motor movement of the tongue, increased by an average of 17% in 60% of participants ($p = 0.056$). Taken together, these data imply a positive effect on speech outcomes following DMQ treatment. Given the predilection of tongue morphology and physiologic deterioration in ALS, these preliminary findings warrant further investigation in a larger cohort of pALS, as they may represent an impact on the fine motor function of the tongue.[32]

Although the patient-reported CNS-BFS and EAT-10 scores improved 4.8% and 13.01%, respectively, following treatment, these improvements were non-significant. These results conflict with a previous study using the

patient-report CNS-BFS following 28 days of DMQ treatment, which demonstrated significant improvements in the total score and sialorrhea, speech and swallowing subdomains.[13] The discrepancy between the results of these two studies is likely attributable to the small sample size of this pilot study, but also underscores the importance of incorporating physiologic speech and swallowing outcomes to detect the likely subclinical changes in motor function that are crucial in driving additional drug study and exploring drug repurposing. This is particularly important in the context of a pharmaceutical intervention that impacts the serotonergic system and feelings of emotional well-being[15] and to identify potential phenotypes of improvement (i.e., sex and disease demographics) in this heterogenous population. To date, no study has incorporated the EAT-10 as an outcome; however, there exist the same limitations of patient-reported tools in interventional ALS trials. While patient-report outcome measures are an important metric to evaluate patient perspective, the findings of the current study suggest that quantitative measures of speech and swallowing are more sensitive to change over time and following intervention, particularly in this pilot trial with a small sample size.[14]

Based on recent evidence, there is a plausible mechanism of action to support the observed functional improvements in speech and swallowing following DMQ treatment. DMQ and a similar, more recently studied compound, pridopidine, have been investigated for their potential therapeutic neuroprotective effects in ALS, as sigma-1 receptor agonists with an impact on serotonin reuptake.[33] Sigma-1 receptors densely populate the brainstem and cerebellum, and serotonin (5-HT) represents most prominent neuromodulator of the swallowing central pattern generator (i.e., nucleus tractus solitarii),[34,35] with animal studies demonstrating impaired swallowing function in mice lacking brain-derived 5-HT.[36,37] There are a density of 5-HT receptors within the nucleus tractus solitarii, thus representing a potential therapeutic target to mitigate speech and swallowing decline and potentially improve these essential functions. This is particularly relevant in the context of ALS, as studies report degeneration of brainstem serotonin neurons in ALS animal models and pALS, and demonstrate hastened disease progression following ablation of the 5-HT2B (serotonin) receptor in the SOD1 animal model.[38,39]

Several limitations of this study need to be highlighted. The trial design has limitations including the short treatment duration, pilot nature of this work and lack of a control group. The treatment duration of 28 days was adopted from the initial positive DMQ treatment trial using a self-report scale as the primary outcome measure.[13] Although this study is the largest to date to include physiologic, validated outcomes of both speech and swallowing in pALS, the sample size was small for a treatment study due to the nature of the funding mechanism. Of note, this study was conducted during the SARS-CoV-2 pandemic which significantly limited recruitment and retention. Finally, execution of a larger study with a control group is necessary to validate the findings of this small but promising dataset and confidently determine that the observed improvements are due to DM/Q treatment.

Conclusions

This trial demonstrated significant improvements in bulbar function as measured by the ALSFRS-R bulbar subscore, quantifiable indices of swallowing efficiency and airway safety, and speech function following 28 days of DMQ treatment in pALS with mild–moderate bulbar impairment. Future work in a larger group of pALS with a control group and open-label extension is needed to understand the long-term impact of DMQ and to advance bulbar treatment options in this challenging patient population.

Author Contributions

LTG contributed to study design, data acquisition, data analysis, and drafting the manuscript. EP, TV, and JW contributed to study design, data analysis, and drafting the manuscript. EL contributed to data acquisition and analysis and drafting the manuscript.

Acknowledgments

Thank you to the pALS and their caregivers for participating in the study and to the ALS Association for awarding the Clinical Management Grant to complete this study.

Conflict of Interest

Nothing to disclose.

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